UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

In re: AVANDIA MARKETING SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION	:	AVANDIA MDL 1871 2007-MD-1871 HON. CYNTHIA M. RUFE
THIS DOCUMENT RELATES TO: ALL ACTIONS	:	

GLAXOSMITHKLINE'S OVERVIEW MEMORANDUM ON *DAUBERT* ISSUES RELATING TO GENERAL CAUSATION

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I. INTRODUCTION

Plaintiffs' experts lack "good grounds" to testify to a reasonable degree of scientific certainty that Avandia can *cause* heart attack. GlaxoSmithKline (GSK) therefore requests that the Court exclude the proposed testimony of plaintiffs' experts on general causation pursuant to the Court's gate-keeping role under Fed. R. Evid. 702 and *Daubert v. Merrell Dow Pharms*., 509 U.S. 579, 590 (U.S. 1993) (proposed expert testimony must be based on good grounds).[1] This Memorandum provides an overview of the issues relating to general causation, namely, can Avandia cause heart attack? GSK is contemporaneously filing motions addressing the opinions of each of the plaintiffs' seven general causation experts.[2] Although there are many common threads, which are discussed in this Memorandum, each expert's opinion is made unreliable by both common and individual flaws.[3]

In 2007, the Food and Drug Administration (FDA) determined that the available data with respect to whether Avandia increases the risk of heart attack were "inconclusive", which is how the data were described in the FDA-approved label for Avandia beginning in November 2007. On July 13-14, 2010, the FDA convened a second Joint Meeting of the FDA's Endocrinologic and Metabolic Drugs Advisory and Drug Safety and Risk Management Committees (Ad Com) bringing together over thirty epidemiologists, cardiologists, statisticians,

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[1] In support of each individual challenge to Plaintiffs' experts, GSK submits a consolidated set of exhibits along with this Memorandum. *See* Exhibit Binders Volume 1 through 6.

[2] Plaintiffs served reports by the following experts on general causation: Donald Austin M.D., Eliot A. Brinton, M.D., Nicholas P. Jewell, Ph.D., Stephen S. Lippman, M.D., Joshua Septimus, M.D., Allan D. Sniderman, M.D., and Brian C. Swirsky, M.D. Two other experts, Suzanne Parisian, M.D. and John L. Guerigian, M.D., primarily address subjects other than general causation, but their reports also contain opinions on general causation that likewise do not meet the *Daubert* standard for reliability.

[3] At this stage, GSK confines its *Daubert* challenge to whether Avandia can cause heart attack as the first trial case *Burford* alleges that Avandia caused the decedent's alleged heart attack. If there are trial cases that allege stroke, fractures, macular edema, or other injuries, GSK will present its *Daubert* challenges with respect to those issues in those cases.

and endocrinologists. For two days, they pored over thousands of pages of data. The Ad Com members did not address the issue that underlies the motions before the Court -- whether the data establish to a reasonable degree of medical certainty that Avandia *causes* heart attack. Nor did they address the less rigorous question of whether Avandia *increases the risk* of heart attack, which was the question as originally framed to the Ad Com. In fact, the Ad Com expressly decided not to answer that question. Rather, the Ad Com rewrote the question to an even lower threshold, akin to what scientists call a signal: whether the data raised "*significant safety concerns*" for ischemic cardiovascular events in patients on Avandia. The Ad Com experts could not agree on this question, as explained below in Section II, and repeatedly noted the fragility and inadequacy of the data in the face of *no statistically significant randomized clinical trial finding an increased risk of heart attack with Avandia.*

Notwithstanding the disagreement and uncertainty among the independent experts selected by FDA, the plaintiffs' witnesses propose to testify that Avandia *does* cause heart attack. Plaintiffs' experts' opinions are not scientifically reliable for the following reasons:

- None of the many randomized clinical trials (RCTs) report a statistically significant increased risk of heart attack in patients taking Avandia;
- Five RCTs show that Avandia does not increase the progression of atherosclerosis. No RCT even suggests that Avandia causes atherosclerosis, which is the principal cause of heart attack;
- Unable to rely on any RCTs, plaintiffs' experts place enormous reliance on meta-analyses of some clinical trials. A meta-analysis is not itself a trial, but rather a statistical pooled analysis of the results of several trials. Plaintiffs' experts ignored the most comprehensive meta-analysis

(involving 164 clinical trials), which concluded that Avandia does not increase the risk of heart attack;

- In addition to selective reliance on some meta-analyses, plaintiffs' experts cherry-pick among observational studies of patients taking Avandia. Patients in these studies were not randomized to Avandia and comparator drugs. Plaintiffs' experts ignore the fact that a majority of the observational studies found no increase in heart attack.

Plaintiffs, of course, must establish not just general causation, but also specific causation, namely, that there is reliable evidence that, but for taking Avandia, plaintiff would not have had a heart attack. Plaintiffs proffer just one expert witness, Nicholas L. DePace, M.D., a cardiologist, to address specific causation in *Burford*, which is the only trial case now before the Court. In a separate motion, GSK has moved to exclude Dr. DePace's testimony. If that motion is granted, it will not be necessary for the Court to address, at least in the near term, GSK's motions to exclude plaintiffs' experts on general causation.[4] A decision on specific causation in *Burford* will be informative for other cases, because at the heart of that motion is the methodology by which an expert could reliably testify that Avandia caused an individual patient's heart attack– the critical issue in all trials.

Submitted with this Memorandum are three appendices, which address in more detail some of the scientific background common to each of the expert-specific motions.[5]

[4] A second case-specific expert in *Burford*, Judy Melinek, M.D., proposes to testify that the plaintiff died from a heart attack and that Avandia increased the risk that he would have a heart attack, but she does not contend that Avandia was the but-for cause of the plaintiff's death. GSK's *Daubert* motion with respect to Dr. Melinek's testimony will be filed on or before September 10, 2010, the deadline for any such motion.

[5] The appendices are: Appendix I, The Role Of Epidemiological Studies In Evaluating Causation; Appendix II, Epidemiological Studies Relating To Avandia and MI; and Appendix III, The Views Of Professional Organizations.

II. THE ISSUE BEFORE THE COURT IS WHETHER PLAINTIFFS' EXPERTS HAVE GOOD GROUNDS FOR THEIR OPINIONS THAT AVANDIA CAN CAUSE HEART ATTACK

Not only must there be "good grounds" for an expert's causation opinion, but the expert must testify to a reasonable degree of scientific certainty – a dual standard.[6] Therefore, in exercising its gate-keeping role under *Daubert*, the Court's analysis will be informed by the legal standard for proof of factual causation.

This standard is different from that which the FDA applies to determine, for example, whether a medicine should remain on the market or whether an additional warning should be added to the label. Even in cases in which FDA has determined to withdraw a medicine from the market for safety reasons or to restrict its use, courts have nevertheless held that plaintiffs' general causation testimony did not meet *Daubert* standards.[7] In a case in which the FDA had withdrawn approval for Parlodel (a lactation suppressant) because of links to stroke, the Eleventh Circuit nevertheless affirmed exclusion of all five of plaintiffs' well-credentialed experts, stating:

> [The FDA's] risk-utility analysis involves a much lower standard than that which is demanded by a court of law. A regulatory agency such as the FDA may choose to err on the side of caution.

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[6] *In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717, 750 (3d Cir. 1994). *See also Daubert v. Merrell Dow Pharms*., 509 U.S. 579, 590 (1993).

[7] *See, e.g., McClain v. Metabolife Int'l*, Inc., 401 F.3d 1233, 1248-1249 (11th Cir. 2005) (finding the FDA's "proposal to severely restrict the sale and distribution of herbal supplements containing ephedrine" to be unreliable evidence of causation because "the court must focus on assessing causation, not on a cost-benefit analysis for restricting the sale and use of a drug"); *Hollander v. Sandoz Pharms. Corp.*, 289 F.3d 1193, 1215 (10th Cir. 2002)("Moreover, the language used in the FDA ruling regarding the withdrawal of Parlodel indicates that the agency did not make a determination that Parlodel causes seizures and strokes. Accordingly, we conclude that the FDA ruling does not establish that there are controverted factual issues as to whether Parlodel caused Ms. Hollanders' stroke."); *Allen v. Pennsylvania Engr'g Corp*., 102 F.3d 194, 198 (5th Cir. 1996) (rejecting experts' reliance on the methodology employed by regulatory agencies because "[t]he agencies' threshold of proof is reasonably lower than that appropriate in tort law, which 'traditionally make[s] more particularized inquiries into cause and effect' and requires a plaintiff to prove 'that it is more likely than not that another individual has caused him or her harm'").

> Courts, however, are required by the *Daubert* trilogy to engage in objective review of the evidence to determine whether it has sufficient scientific basis to be considered reliable.[8]

The causation standard that underlies the Court's *Daubert* analysis is also different from the standard a clinician would apply in determining whether to prescribe a drug in light of alleged safety concerns and the availability of alternative, purportedly safer, drugs.[9]

The distinctions among these different standards were demonstrated at the two-day July 2010 Ad Com meeting. The initial question that the Ad Com was to address was "do you find that rosiglitazone increases the risk of ischemic cardiovascular events . . . ."[10] The Ad Com voted not to answer that question.[11] The question the Ad Com considered and answered was not whether Avandia has been shown to *cause* heart attack, nor whether Avandia increases the risk of heart attack, but rather whether the data were sufficient "to raise significant safety concerns for ischemic cardiovascular events in patients with type 2 diabetes relative to non-TZD anti-diabetic agents."[12] Fifteen of the thirty-three members were not convinced that the data even raised "significant safety concerns." And of the eighteen who felt that there were "significant safety concerns," nearly all made it clear in their comments that they believed only

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[8] *Rider v. Sandoz Pharms. Corp.*, 295 F.3d 1194, 1201 (11th Cir. 2002).

[9] *Siharath v. Sandoz Pharm. Corp.*, 131 F. Supp. 2d 1347, 1372 (N.D. Ga. 2001); *Norris v. Baxter Healthcare Corp*., 397 F.3d 878, 887 (10th Cir. 2005) ("We cannot allow the jury to speculate based on an expert's opinion which relies only on clinical experience in the absence of showing a consistent, statistically significant association between breast implants and systemic disease"); *Hollander v. Sandoz Pharms. Corp.*, 289 F.3d 1193, 1213 (10th Cir. 2002) (affirming exclusion of plaintiffs' experts whose causation opinions were based on "speculative leaps," notwithstanding the fact that "[t]he data on which they rely might well raise serious concerns in conscientious clinicians seeking to decide whether the benefits of the drug outweigh its risks").

[10] July 14, 2010 FDA Advisory Committee Transcript ("July 14 Ad Com Tr."), at 75 (attached as Exhibit 71).

[11] *Id*. at 77.

[12] *Id.* at 83. The Ad Com answered a similar question comparing Avandia to Actos, another drug in the same thiozoladinedione (TZD) class. *Id.* at 85.

that there was a "safety signal"[13] or that the data did "raise concerns."[14] In addition, numerous Ad Com members stated that the data on cardiovascular risk did not show "a clear signal," that the data were "inconclusive" and "not definitive," and that the "data is mostly trends, not statistically significant."[15]

Similarly, with respect to the alleged association between Avandia and mortality, the question the Ad Com answered was not whether Avandia *causes* mortality, but rather whether the "data are sufficient to raise significant safety concerns for mortality in patients with type 2 diabetes relative to non-TZD anti-diabetic agents."[16] Thirty-one of the Ad Com members found that the mortality data did *not* raise significant safety concerns; only two found that the data did so.[17] This is particularly relevant to *Burford*, in which the plaintiff died.

The Chairman of the Ad Com, Dr. Kenneth Burman, Chief Endocrine Section, Washington Hospital Center, summarized the evidence when he explained his vote to keep Avandia on the market:

> …. when considering the totality of the data, I think the preponderance of evidence, although not definitive, suggest that rosiglitazone is safe. It is correct that there is an alternative agent in the class that can be used. But I believe we should make our decision based on the evidence at hand.[18]

[13] *Id.* at 87, 90, 93, and 94.

[14] *Id.* at 91.

[15] *Id.* at 90.

[16] *Id.* at 97.

[17] *Id.* at 97.

[18] *Id.* at 123.

Dr. Sanjay Kaul, an Ad Com member and the cardiologist who chaired a joint American Heart Association and American College of Cardiology panel that considered the safety of Avandia, summarized the views of many Ad Com members when he said:

> In my opinion, data are inconclusive, presenting neither an increase nor a decrease, and risk can't be established by these analyses. The incriminating evidence comes from meta-analyses that have safety signals that are not sufficiently discernible from a null effect. I do not consider a meta-analytic p value of 0.05 or less to be strong evidence. And I have a healthy respect for what meta-analyses can do or what they cannot do. They're mostly good for asking questions not answering them.
>
> So, while I'm not persuaded by the evidence presented to implicate the drug, I'm also not entirely reassured by the evidence presented to exonerate it. There still is currently not enough data to support the choice of a specific TZD [over another TZD].[19]

In light of all the data, some of which we discuss below, and its evaluation by the Ad Com, there is clearly no general acceptance in the medical community that Avandia *causes* heart attack; on the contrary, there is agreement that the existing data are fragile and inconclusive. Indeed, no professional organization that has considered the issue has concluded that Avandia causes heart attack, as shown in Appendix III.

III. THE RELEVANT *DAUBERT* FACTORS

A. The Court As A Gate-Keeper

Expert opinion must be based on scientifically reliable evidence.[20] The Court's role under *Daubert* and Rule 702 is to assess plaintiffs' experts' methodology and the conclusions they draw from the data. A district court has an obligation as "gatekeeper" to screen

[19] *Id.* at 88.

[20] *Daubert v. Merrell Dow Pharms.*, 509 U.S. 579, 589 (1993).

proffered testimony to insure that it is both relevant and reliable.[21] Under *Daubert*'s reliability prong, an expert's opinion "'must be based on the methods and procedures of science,' rather than on 'subjective belief or unsupported speculation.'"[22] Thus, "the expert must have 'good grounds' for his or her belief."[23]

Of particular importance here is the Supreme Court's observation that "conclusions and methodology are not entirely distinct from one another," and "[a] court may conclude that there is simply too great an analytical gap between the data and the opinion proffered."[24] As the Supreme Court explained, "[t]rained experts commonly extrapolate from existing data. But nothing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence that is connected to existing data only by the *ipse dixit* of the expert."[25]

B. Plaintiffs Have The Burden Of Proof

Plaintiffs have the burden of demonstrating the admissibility of the proposed testimony under *Daubert*.[26] That burden is not lessened by any paucity of data:

> . . . the non-existence of good data does not allow expert witnesses to speculate or base their conclusions on inadequate supporting science. In cases where no adequate study shows the link between a substance and a disease, expert testimony will generally be

[21] *Daubert*, 509 U.S. at 589-92; *Pineda v. Ford Motor Co.*, 520 F.3d 237, 243 (3d Cir. 2008).

[22] *In re Paoli*, 35 F.3d at 742.

[23] *Id., quoting Daubert*, 509 U.S. at 590.

[24] *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997).

[25] *Id.*

[26] *See Daubert*, 509 U.S. at 592 n.10; *United States v. Monaghan*, 648 F. Supp. 2d 658, 660 (E.D. Pa. 2009).

> inadmissible, even if there are hints in the data that some link might exist.[27]

A related and significant principle is that "[t]he courtroom is not the place for scientific guesswork, even of the inspired sort. Law lags science; it does not lead it.'"[28]

IV. NUMEROUS FACTORS ESTABLISH THE UNRELIABILITY OF THE PROPOSED TESTIMONY OF PLAINTIFFS' GENERAL CAUSATION EXPERTS

Despite extensive study and consideration of the data, not one professional association has reached the same conclusion as plaintiffs' experts. *See* Appendix III. This alone establishes the unreliability of their theories and methods. In this section, we address the type of studies that the experts purport to rely on, as well as the background rate of heart attack in the diabetic population. We then identify the main flaws in the experts' methods.

A. Epidemiological Background

The different types of epidemiological studies are described in the *Reference Manual on Scientific Evidence* (Fed. Jud. Ctr. 2d ed. 2000) (*Reference Manual*) at 333-400.[29] The "gold standard" for studies of a medicine is a randomized clinical trial (RCT). An RCT is "an experimental study in which subjects are randomly assigned to one of two groups: one group exposed to the agent of interest and the other not exposed."[30] Plaintiffs' experts agree.[31]

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[27] *Perry v. Novartis Pharms. Corp.*, 564 F. Supp. 2d 452, 467-68 (E.D. Pa. 2008).

[28] *Johnson v. SJP Mgmt. LLC*, 2009 U.S. Dist. LEXIS 11272 (E.D. Pa. Feb. 12, 2009) (quoting *Rosen v. Ciba-Geigy Corp.*, 78 F.3d 316, 318 (7th Cir. 1996); *Perry v. Novartis Pharms. Corp.*, 564 F. Supp. 2d at 452. (quoting *Rosen v. Ciba-Geigy Corp.*, 78 F.3d 316, 318 (7th Cir. 1996).

[29] A more complete discussion of the role of epidemiology in establishing a cause and effect relationship is found in Appendix I.

[30] Federal Judicial Center, *Reference Manual on Scientific Evidence* 338 (2d ed. 2000) ("*Reference Manual*") (attached as Exhibit 128).

Avandia has been researched extensively in RCTs. Of the hundreds of RCTs done with Avandia over the past two decades, not one RCT shows a statistically significant increase in the risk of heart attack with Avandia.

In the absence of any RCT supporting their position, plaintiffs' experts rely on meta-analyses and observational studies. A meta-analysis is not a clinical study; it is, rather, a retrospective analysis that looks for statistical associations by pooling data from studies that may differ in terms of design, purpose and endpoints.[32] The findings of a meta-analysis are therefore less reliable than those of a well-designed RCT, as plaintiffs' experts acknowledge.[33]

Observational studies "'observe' a group of individuals who have been exposed to an agent of interest . . . and compare them with another group of individuals who have not been so exposed."[34] Observational studies, unlike RCTs, do not randomly assign patients to the drug of interest and comparators. Therefore, they cannot directly control for factors other than the exposure that may contribute to the relationship under study, and such confounding factors must be considered in interpreting the results of observational studies.[35]

(continued...)

[31] *See e.g.*, Deposition Transcript of Donald F. Austin, M.D., MPH ("Austin Dep. Tr."), Apr. 6, 2010, at 196 (attached as Exhibit 36); Deposition Transcript of Eliot A. Brinton, M.D. ("Brinton Dep. Tr."), Apr. 28, 2010, at 301 (attached as Exhibit 37).

[32] *Reference Manual* at 380 (Ex. 128).

[33] *See e.g.*, Supplemental Generic Expert Report of Allan Sniderman, M.D., Mar. 15, 2010, at 3 (attached as Exhibit 17) ("I agree that, as a general proposition, randomized clinical trials are more powerful tools – or put differently less susceptible to error – than meta-analyses which in turn are superior to observational studies"); Deposition transcript of Nicholas L. DePace, M.D, *Burford v. GSK*, MDL No. 1871, Case No. 2:07-cv-05360-CMR, Apr. 17, 2010, at 180 (attached as Exhibit 39) (recognizing that there is a "hierarchy of scientific proof," with randomized controlled trials at the top, followed by meta-analyses, and then observational studies); Generic Expert Report of Eliot A. Brinton, M.D., Jan. 15, 2010 ("Brinton Report"), at 33 (attached as Exhibit 3).

[34] *Reference Manual* at 339 (Ex. 128).

[35] *Id.* at 380.

B. Medical Background

The epidemiological studies of Avandia must be understood in the context of the patient group for which Avandia is indicated for use – Type 2 diabetics. As detailed below, there is a substantial background risk of heart attack in patients with diabetes and they have a two to four-fold risk of cardiovascular disease compared to the general population. This makes it harder to detect a true increase in risk caused by a drug taken to treat diabetes, especially a risk that is relatively small. Dr. Janet Woodcock (Director of the FDA's Center for Drug Evaluation and Research) commented on the difficulty of seeing a small increased risk in a population with a significant background risk at the Ad Com:

> Here, we're struggling more because this is a hypothesis or a potential for a small in numerical terms, although not in population terms, increase in a risk over a background risk, something that's more difficult to uncover.[36]

Diabetes is a "coronary risk equivalent," meaning that patients with diabetes and patients with a prior heart attack are at the same high risk of having a future heart attack.[37] "[M]ost patients with diabetes have some degree of heart disease."[38] And "75 or 80% of diabetic mortality is attributed to coronary artery disease."[39] A majority of diabetics who suffer heart attacks also live with other risk factors for heart attack, including high blood pressure, smoking, metabolic syndrome,[40] elevated LDL (bad cholesterol), low HDL (good cholesterol), high

[36] July 14 Ad Com Tr. at 113 (Ex. 71).

[37] Deposition Transcript of Brian C. Swirsky, M.D., FACC, ("Swirsky Dep. Tr."), Apr. 23, 2010, at 149 (attached as Exhibit 47).

[38] Swirsky Dep. Tr. at 149 (Ex. 47).

[39] *Id.* at 157-58.

[40] "Metabolic syndrome" is defined as the presence of three or more of the following risk factors: "abdominal obesity, high triglycerides, low HDL, high blood pressure, and elevated fasting glucose." Brinton Dep. Tr. at 231 (Ex. 37).

triglycerides (another fat in the blood), obesity, sedentary lifestyle, family history, advancing age, and male sex.[41]

The medical context and the difficulty in uncovering a small increased risk is illustrated by Dr. Nissen's 2010 meta-analysis. In the populations studied, 17,258 patients took Avandia and 159 had a heart attack (0.92 %); in contrast, 14,449 patients did not take Avandia and 136 had a heart attack (0.94 %).[42] Stated differently, this means that among patients not taking Avandia heart attacks occurred in 94 per 10,000 patients, whereas in patients taking Avandia heart attacks occurred in 92 per 10,000 patients. Because estimates of small effects are sensitive to particular statistical techniques, reliably determining a small increase in the risk of heart attack (such as that reported by Nissen) requires investigation in long-term, randomized clinical trials.

C. No Randomized Clinical Trial Shows A Statistically Significant Increase In Heart Attack In Patients Taking Avandia

Plaintiffs' experts concede that *no RCT has shown a statistically significant increased risk of heart attack in Avandia patients*.[43] There are several long-term trials of Avandia that address cardiovascular safety, three of which we describe briefly below. While conceding that no RCT supports their conclusions, plaintiffs' experts selectively reference the RCTs to find support for their opinions. The experts criticize the design and conduct of the long-

[41] Deposition Transcript of Stephen S. Lippman, M.D., Ph.D. ("Lippman Dep. Tr."), April 15, 2010, at 286-88 (attached Exhibit 43); Brinton Dep. Tr. at 231-32 (Ex. 37).

[42] Nissen, SE, Wolski K, *Rosiglitazone Revisted: An Updated Meta-analysis of Risk for Myocardial Infarction and Cardiovascular Mortality*, ARCH INTERN MED. (June 2010) (published online) (attached as Exhibit 124).

[43] *See e.g.*, Brinton Dep. Tr. at 283-84 (Ex. 37) (Q: ". . . Is there any randomized controlled trial in which patients are randomized to receive Avandia where there's a statistically significant increase in heart attack in patients taking Avandia?" A: "No."); Austin Dep. Tr. at 200 (Ex. 36).

term trials, but they rely on data from the trials as part of the *Nissen* and *Singh* meta-analyses to bolster their views, discussed at Section IV.D below.[44]

1. The RECORD trial[45]

The RECORD trial is the *only* large RCT specifically designed to evaluate the cardiovascular safety of Avandia. The trial was required by European regulators and supervised by independent researchers. The trial tracked patients over 5 to 7 years of follow-up by comparing patients taking Avandia plus either metformin or a sulfonylurea (oral, generic diabetes medication) to patients taking these two other drugs in combination. All cardiovascular events were adjudicated by independent evaluators blinded to the treatment received. In the words of plaintiffs' expert Dr. Brinton:

> I think that it could be said that the RECORD trial stands head and shoulders above other studies, other single randomized clinical trials of Avandia in the fact that it was a randomized trial in which the use of rosiglitazone [was] randomized, and it was a study in which the primary endpoint was cardiovascular in nature and it was prespecified and events were adjudicated.[46]

The RECORD trial showed no increased risk of cardiovascular death or hospitalization, and no statistically significant increase in the risk of heart attack in the patients treated with Avandia as compared to the controls.[47]

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[44] *See e.g.*, Austin Dep. Tr. at 219-20; 236-37, 277 (Ex. 36); Swirsky Dep. Tr. at 296-97 (Ex. 47); Deposition Transcript of Nicholas P. Jewell, Ph.D, ("Jewell Dep. Tr."), Mar. 10, 2010, at 273 (attached as Exhibit 42).

[45] Philip D. Home *et al.*, for the RECORD Study Team, *Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomized, open-label trial*, 373 LANCET 2125 (2009) (attached as Exhibit 105).

[46] Brinton Dep. Tr. at 348 (Ex. 37)

[47] Home, 373 LANCET 2125 (HR 1.14; 95% CI 0.80 – 1.63) (Ex. 105).

Plaintiffs' experts attack RECORD on several different grounds. It is undisputed, however, that the design of the trial was approved by European regulators interested in evaluating cardiovascular risk, patients were randomized to Avandia and comparator drugs; over 4,000 patients were studied, and the majority were followed for over 5.5 years.[48] RECORD was the subject of extensive discussion at the recent Ad Com. The senior FDA physician to address the study (Dr. Ellis Unger) concluded by saying: "the results of RECORD do not substantiate the findings from the Nissen-Wolski meta-analysis of myocardial infarction and cardiovascular death."[49]

2. The DREAM trial[50]

DREAM was a double-blind placebo-controlled trial designed to evaluate whether Avandia reduced the development of type 2 diabetes in patients at risk for diabetes (but who did not have a diagnosis of diabetes). Patients treated with Avandia had a statistically significant reduction in progression to diabetes. There was no statistically significant increase in heart attack in patients taking Avandia.

3. The ADOPT trial[51]

ADOPT was a double-blind RCT in patients with newly-diagnosed diabetes to assess the effect of Avandia, as compared to other standard glucose-lowering therapies**,** in maintaining long-term glycemic control. Adverse events, including heart attack, were identified

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[48] *Id.*

[49] July 13, 2010 FDA Advisory Committee Transcript ("July 13 Ad Com Tr."), at 58 (attached as Exhibit 70).

[50] *See* Gerstein HC, Yusuf S, et al.; part of DREAM Trial Investigators, *Effect of Rosiglitazone on the Frequency of Diabetes in Patients with Impaired Glucose Tolerance or Impaired Fasting Glucose: A Randomized Controlled Trial,* 368 LANCET 1096 (2006) (attached as Exhibit 98).

[51] *See* Steven E. Kahn et al., for the ADOPT Study Group, *Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy*, 355 NEW ENGL. J. MED. 2427 (2006) (attached as Exhibit 109).

from investigator reports, and GSK and FDA each computed hazard ratios based on these data. Both GSK and FDA found non-significant hazard ratios for heart attack compared to the other therapies. Like the other large, long-term RCTs, there was no statistically significant increase in heart attack in patients taking Avandia.[52]

Other RCTs are consistent, as explained in Appendix II.

D. Meta-Analyses Do Not Provide Scientifically Reliable Support For Plaintiffs' Experts' Opinion That Avandia Causes Heart Attack.

Plaintiffs' experts rely heavily on meta-analyses by *Nissen* and *Singh*, which contain significantly overlapping underlying data.[53] The findings of a meta-analysis are less reliable than those of a well-designed RCT, and meta-analyses are generally considered "hypothesis generating."[54] The *Reference Manual* states that the problems of meta-analysis "have been so frequent and so deep, and overstatements of conclusions so extreme, that one

[52] Dr. Austin criticized the ADOPT study, which he admits did not report a statistically significant increased risk of MI in patients taking Avandia (Austin Dep. Tr. at 236-37, Ex. 36), on the basis that it "merely collected unadjudicated cardiovascular events." *See* Generic Expert Report of Donald Austin, M.D., Jan. 15, 2010 ("Austin Report"), at 4 (attached as Exhibit 1). But Dr. Austin relied on the Nissen meta-analysis even though most of the trials in *Nissen* did not centrally adjudicate cardiovascular outcomes, and he relied on the *Nissen* and *Singh* meta-analyses even though those studies included the unadjudicated ADOPT study data. *See* Austin Dep. Tr. at 292; 277 (Ex. 36). Dr. Austin also criticized the ADOPT study on the basis that the study "was not designed to assess cardiovascular safety." Austin Report, at 4 (Ex. 1). But Dr. Austin relied on the results of the Nissen meta-analysis even though none of the randomized controlled trials in that meta-analysis were designed to assess cardiovascular outcomes. *See* Austin Dep. Tr. at 222 (Ex. 36).

[53] *See, e.g.*, Lippman Dep. Tr. at 241 (Ex. 43) ("Q: So tell me which of these observational studies you cited to support the idea that Avandia causes heart attack as opposed to a possible mechanism that might explain your opinion that Avandia causes heart attack? Do you understand my question?" A: "Yes, I understand your question. And what I -- in the report, what I cite primarily is -- is the Nissen analysis."); Swirsky Dep. Tr. at 292-293 (Ex. 47) (acknowledging that there is a 75% overlap between the data used in the Nissen and Singh meta-analyses).

[54] Swirsky Dep. Tr. at 274-75 (Ex. 47).

might well conclude that there is something seriously and fundamentally wrong with the method."[55] These problems are present here.

1. The *Nissen* Meta-Analysis Does Not Show That Avandia Causes Heart Attack

Dr. Steven Nissen's meta-analysis initially reviewed forty-two clinical trials, and was published in May 2007.[56] (This is the study relied on by the experts in their initial reports and at their depositions). Dr. Nissen reported that Avandia increased the risk of heart attack by a factor of 1.43.[57] *He did not conclude that Avandia causes heart attack*; he recommended, rather, that "patients and providers should carefully consider the *potential* risks of rosiglitazone in the treatment of type 2 diabetes."[58]

On June 28, 2010, the *Archives of Internal Medicine* published an updated analysis by Dr. Nissen.[59] Dr. Nissen's 2010 analysis pooled data from 56 trials in which patients had taken Avandia. (Many of these trials were short-term and were not designed to study cardiovascular safety, but they did report heart attacks and other events occurring during the

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[55] *Reference Manual* at 381 n.127 (quoting John C. Bailar III, *Assessing Assessments*, 277 SCIENCE 528, 529 (1997)) (Ex. 128).

[56] Steven E. Nissen & Kathy Wolski, *Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes*, 356 NEW ENG. J. MED. 2457 (2007) (attached as Exhibit 123).

[57] The Singh meta-analysis, which pooled data from four long-term clinical trials, found a statistically significant increased risk of heart attack in the same range as Nissen. *See* Singh S, Loke YK, Furberg CD, *Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis*, 298 JAMA 1189 (2007) (attached as Exhibit 131). This was not surprising considering that, as plaintiffs' experts acknowledge, the data that were analyzed in the Singh meta-analysis largely overlapped the Nissen data. *See, e.g.*, Swirsky Dep. Tr. at 292-93 (Q: "Okay. Well, for instance Dr. Singh's meta-analysis and Dr. Nissen's meta-analysis, do you understand that Dr. Singh's and Dr. Nissen's analysis have a 75 percent overlap?" A: "I do understand there is overlap, yes"). However, the *Singh* meta-analysis relied upon interim rather than the final RECORD data and used unadjudicated rather than adjudicated data from the ADOPT study. *See* Appendix II.

[58] Nissen, 356 NEW ENG. J. MED. at 2470 (emphasis added) (Ex. 123).

[59] Steven E. Nissen and Kathy Wolski, *Rosiglitazone Revisited: An Updated Meta-analysis of Risk for Myocardial Infarction and Cardiovascular Mortality*, ARCH INTERN MED (June 2010) (published online) (attached as Exhibit 124).

trials). When the trials were analyzed separately, no statistically significant increase in the risk of heart attack was observed in patients treated with Avandia. When the data were combined, however, *Nissen* reported that Avandia increased the risk of heart attack by a factor of 1.28.[60] The conclusion of the 2010 *Nissen* meta-analysis is that the results "suggest an unfavorable benefit to risk ratio for rosiglitazone use."[61] Thus, like his 2007 article, Dr. Nissen's 2010 article did *not* state that Avandia has been proven to cause heart attack. Where data merely "suggest" an association, an expert's causation opinion falls short of the required *Daubert* standard.[62]

Dr. Nissen presented his meta-analyses to the Ad Com. Dr. Sanjay Kaul, a cardiologist, told Dr. Nissen that he found the data "fragile" and "deserving of a conservative, or what I call frugal, interpretation, not liberal interpretation." Dr. Nissen responded that Dr. Kaul was "absolutely right."[63] Dr. Nissen went on to state that "the absence of evidence" of Avandia's ischemic cardiovascular risk "is certainly not evidence of absence."[64] Even assuming that Dr. Nissen is correct and that there is insufficient evidence that Avandia does not cause ischemic cardiovascular events, this does not help plaintiffs meet their burden of proving causation.[65] On the other hand, the fact that arguably the most prominent critic of Avandia, and

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[60] This does not mean that patients who take Avandia have a 28% risk of having a heart attack; rather, it signifies that if a person's "background" risk of heart attack were 2% (*i.e.*, 2 chances in 100), the risk, if Nissen were correct, would be 1.28 times 2%, or 2.56% (*i.e.*, 2.56 chances in 100).

[61] Nissen, ARCH INTERN MED, (June 2010) (published online) (Ex. 124).

[62] *Milward v. Acuity Specialty Prods. Group, Inc.*, 664 F. Supp. 2d 137, 149 (D. Mass. 2009) ("A 'suggestion' may give rise to a plausible hypothesis, but not a reliable inference).

[63] July 13 Ad Com Tr., at 141 (Ex. 70).

[64] *Id.*

[65] *See e.g.*, *Soldo v. Sandoz Pharm. Corp.*, 244 F. Supp. 2d 434, 558 (W.D. Pa. 2003) (excluding expert whose approach "would turn Rule 702 and Daubert on their heads by allowing the *absence* of reliable testing and data to support a causation opinion.") (emphasis in the original).

the primary author of two meta-analyses that are the centerpiece of plaintiffs' evidence of Avandia's alleged cardiovascular risk, acknowledged the "absence of evidence" of such risk, speaks volumes about the lack of scientific basis for plaintiffs' claims.

2. Other Meta-Analyses Do Not Show That Avandia Causes Heart Attack

Besides *Nissen* and *Singh*, there have been several other meta-analyses including those done by GSK,[66] the FDA,[67] and researchers not associated with GSK.[68] The more comprehensive of these did not find a statistically significant increase in heart attack in patients taking Avandia. *Mannucci*, who included 164 trials in his meta-analysis, concluded that "there is no evidence of increased risk of myocardial infarction or cardiovascular mortality in patients treated with rosiglitazone."[69]

Plaintiffs' experts have made little or no effort to explain why they rely so heavily on the two *Nissen* and *Singh* meta-analyses, when a number of other meta-analyses have reached different results.[70] It is unscientific to rely on selected data and to ignore other relevant data that point in the other direction. As a Delaware judge stated recently: "Simply stated, the expert

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[66] Cobitz A, Zambanini A, et al., *A retrospective evaluation of congestive heart failure and myocardial ischemia events in 14,237 patients with type 2 diabetes mellitus enrolled in 42 short-term, double-blind, randomized clinical studies with rosiglitazone*, 17 PHARMACOEPIDEMIOL DRUG SAF 769 (2008) (attached as Exhibit 65).

[67] In 2010, the FDA updated its 2007 meta-analysis, using only the short-term trials, most of which compared Avandia to placebo only, i.e. excluding RECORD, DREAM and ADOPT. In this analysis, the FDA found a statistically significant increase in risk of heart attack in patients taking Avandia.

[68] Diamond GA, Bax L, Kaul S, *Uncertain effects of rosiglitazone on the risk for myocardial infarction and cardiovascular death*, 147 ANN INTERN MED 578 (2007) (attached as Exhibit 66); Monami M, Marchionni N, Mannucci E, *Winners and losers at the rosiglitazone gamble A meta-analytical approach at the definition of the cardiovascular risk profile of rosiglitazone*, 82 DIABETES RES CLIN PRACT 48 (2008) (attached as Exhibit 118); Edoardo Mannucci et al., *Cardiac safety profile of rosiglitazone: A comprehensive meta-analysis of randomized clinical trials*, INT. J. CARDIOL., e-publication (2009) (attached as Exhibit 115).

[69] Mannucci et al., INT. J. CARDIOL (2009) (Ex. 115).

[70] *See, e.g.*, Swirsky Dep. Tr. at 253 (Ex. 47) (stating that he "chose" the Nissen meta-analysis over the Diamond meta-analysis based on the fact that Nissen is "a known entity for [him]").

cannot accept some but reject other data from the medical literature without explaining the bases for her acceptance or rejection."[71] Similarly, Judge Kaplan in his opinion in *Rezulin* excluding general causation testimony of "silent liver injury" noted that "courts have excluded expert testimony 'where the expert selectively chose his support from the scientific landscape.'"[72]

E. Observational Studies Do Not Provide Scientifically Reliable Support For Plaintiffs' Experts' Opinions That Avandia Causes Heart Attack

In addition to their selective reliance on certain meta-analyses, plaintiffs' experts cite some observational studies, which are reviews of data relating to patients who were not randomized to Avandia or any comparator.[73] Thus, there is a potential for bias and confounding that can make the findings of such studies unreliable.[74] But the flaws in the plaintiffs' experts' approach go far beyond their reliance on observational studies in the face of RCTs that do not support their opinions.

1. Plaintiffs' experts have relied on only some of the observational studies, and they apply inconsistent criteria in rejecting studies that do not support their opinions

There are twenty-three observational studies that have assessed the possible relationship between Avandia and heart attack. The reported findings are inconsistent and

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[71] *Scaife v. Astrazeneca LP*, 2009 Del. Super. LEXIS 216, 73-74 (Del. Super. Ct. June 9, 2009) (citations and footnotes omitted).

[72] *In re Rezulin Prods. Liab. Litig.*, 369 F. Supp. 2d 398, 425 (S.D.N.Y. 2005) (Rezulin was a diabetes drug in the same class as Avandia and Actos); s*ee also In re Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig*., 524 F. Supp. 2d 1166, 1176 (N.D. Cal. 2007) (excluding expert for "cherry-picking observational studies that support his conclusion and rejecting or ignoring the great weight of the evidence that contradicts his conclusion. Dr. Doherty's opinion does not reflect scientific knowledge, is not derived by the scientific method, and is not 'good science;' it is therefore inadmissible.").

[73] *See* Appendix II at 2; *Reference Manual* at 338 ("[R]andomization minimizes the likelihood that there are differences in relevant characteristics between those exposed to the agent and those not exposed.") (Ex. 128).

[74] *See, e.g.*, Generic Expert Report of Nicholas P. Jewell, Ph.D., Jan. 15, 2010. ("Jewell Report"), at 34-39 (attached as Exhibit 10).

inconclusive: nine showed a statistically significant increased risk of heart attack compared to other oral anti-diabetic drugs or compared specifically to pioglitazone;[75] thirteen found no statistically significant association;[76] and one found a statistically significant *protective*

[75] Brownstein JS, et al, *Rapid identification of myocardial infarction risk associated with diabetes medications using electronic medical records*, 33 DIABETES CARE 526 (2010) (attached as Exhibit 62); Gerrits et al., *A Comparison of Pioglitazone and Rosiglitazone for Hospitalization for Acute Myocardial Infarction in Type 2 Diabetes*, 16 PHARMACOEPIDEMIOLOGY DRUG SAF. 1065 (2007) (attached as Exhibit 96) ; Hsiao, F. et al., *Thiazolidinediones and Cardiovascular Events in Patients with Type 2 Diabetes Mellitus: A Retrospective Cohort Study of Over 473,000 Patients Using the National Health Insurance Database in Taiwan*, 32 DRUG SAFETY 675 (2009) (attached as Exhibit 106); Koro CE, Fu Q, Stendar M. *An assessment of the effect of thiazolidinedione exposure on the risk of myocardial infarction in type 2 diabetic patients*, 17 PHARMACOEPIDEMIOL DRUG SAF 989 (2008) (attached as Exhibit 111); Lipscombe et al., *Thiazolidinediones and cardiovascular outcomes in older patients with diabetes*, 298 JAMA 2634 (2007) (attached as Exhibit 113); Ramirez Sp, et al., *Rosiglitazone is associated with mortality in chronic hemodialysis patients*, 20 J AM SOC NEPHROL 1094 (2009) (attached as Exhibit 127); Shaya, F. et al., *Thiazolidinediones and Cardiovascular Events in High-Risk Patients with Type-2 Diabetes Mellitus*, 34 P&T 490 (2009) (attached as Exhibit 130); Vanasse, A., et al., *Stroke and Cardiovascular Morbidity and Mortality Associated with Rosiglitazone Use in Elderly Diabetic Patients*, 6 DIAB VASC DIS RES 87 (2009) (attached as Exhibit 138); Ziyadeh N, et al., *The thiazolidinediones rosiglitazone and pioglitazone and the risk of coronary heart disease: a retrospective cohort study using a US health insurance database*, 31 CLIN THER 2665 (2009) (attached as Exhibit 141).

[76] Bilik, D. et al., *Thiazolidinediones and Fractures: Evidence from Translating Research into Action for Diabetes*, 95 J CLIN ENDOCRINOL METAB 0000-0000 (2010) (attached as Exhibit 59); Casscells SW, et al., *A comparison of select cardiovascular outcomes by antidiabetic prescription drug classes used to treat type 2 diabetes among Military Health System beneficiaries, fiscal year 2003-2006*, 15 AM J THER 198 (2008) (attached as Exhibit 64); Dore DD, et al. *Association between extent of thiazolidinedione exposure and risk of acute myocardial infarction*, 29 PHARMACOTHERAPY 775 (2009) (attached as Exhibit 67); Dormuth CR, et al., *Rosiglitazone and myocardial infarction in patients previously prescribed metformin*, PLOS ONE (2009) (attached as Exhibit 68); Graham, DJ, et al., *Risk of Acute Myocardial Infarction, Stroke, Heart Failure, and Death in Elderly Medicare Patients Treated With Rosiglitazone or Pioglitazone*, 304(4) JAMA. 411 (2010) (attached as Exhibit 99); Habib ZA, et al., *Relationship between thiazolidinedione use and cardiovascular outcomes and all-cause mortality among patients with diabetes: a time-updated propensity analysis*, 18 PHARMACOEPIDEMIOL DRUG SAF 437 (2009) (attached as Exhibit 102); Juurlink DN, et al., *Adverse cardiovascular events during treatment with pioglitazone and rosiglitazone: population based cohort study*, 339 BMJ b2942 (2009) (attached as Exhibit 108); McAfee AT, et al., *Coronary heart disease outcomes in patients receiving antidiabetic agents*, 16 PHARMACOEPIDEMIOL DRUG SAF 711 (2007) (attached as Exhibit 117); Pantalone KM, et al., *The risk of developing coronary artery disease or congestive heart failure, and overall mortality, in type 2 diabetic patients receiving rosiglitazone, pioglitazone, metformin, or sulfonylureas: a retrospective analysis*, 46 ACTA DIABETOL 145 (2009) (attached as Exhibit 125); Stockl KM, et al., *Risk of acute myocardial infarction in patients treated with thiazolidinediones or other antidiabetic medications*, 18 PHARMACOEPIDEMIOL DRUG SAF 166 (2009) (no association observed with current rosiglitazone use) (attached as Exhibit 134); Tzoulaki I, et al., *Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database*, 339 BMJ b4731 (2009) (attached as Exhibit 137); Walker AM, Koro CE, Landon J, *Coronary heart disease outcomes in patients receiving antidiabetic agents in the PharMetrics database 2000-2007*, 17 PHARMACOEPIDEMIOL DRUG SAF 760 (2008) (attached as Exhibit 139); Winkelmayer WC, et al., *Comparison of cardiovascular outcomes in elderly patients with diabetes who initiated rosiglitazone vs pioglitazone therapy*, 168 ARCH INTERN MED 2368 (2008) (attached as Exhibit 140).

association.[77] Plaintiffs' experts nevertheless rely on certain of the observational studies which report an increased risk of heart attack in patients on Avandia while ignoring others that do not.[78] This is not good science and cannot support an expert's opinion under Fed. R. Evid. 702.[79]

F. There Are Inconsistencies Within And Between The Studies On Which Plaintiffs' Experts Rely

The studies on which plaintiffs' experts rely cannot provide scientifically reliable support for their opinions for the further reason that the studies are not consistent within or among themselves, and plaintiffs' experts have not explained the inconsistencies. For example, two of the most recent published studies are by authors frequently cited by plaintiffs' experts: Dr. Steven Nissen and Dr. David Graham. In his 2010 meta-analysis, Dr. Nissen found an increased risk for heart attack of 28%, but no increased risk of cardiovascular death.[80] Dr. Graham, in a study of Medicare patients, did not find any difference in the risk of heart attack between patients taking Avandia and those taking Actos, but he did find an increased risk of stroke, heart failure and all-cause mortality.[81] Dr. Graham and his co-authors admitted that they "were unable to determine whether one or both thiazolidinediones increase or decrease the absolute risk of any outcome…."[82] In other words, although Dr Graham and his co-authors acknowledge that their

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[77] Margolis DJ, Hoffstad O, Strom BL, *Association between serious cardiac outcomes and medications used to treat diabetes*, 17 PHARMACOEPIDEMIOL DRUG SAF 753 (2008) (attached as Exhibit 116).

[78] *See, e.g.*, Swirsky Dep. Tr. at 335 (Ex. 47); Brinton Dep. Tr. at 320-21-321:13 (Ex. 37).

[79] *See In re Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig.*, 524 F. Supp. 2d 1166, 1176 (N.D. Cal. 2007) (excluding expert for "cherry-picking observational studies that support his conclusion and rejecting or ignoring the great weight of the evidence that contradicts his conclusion. Dr. Doherty's opinion does not reflect scientific knowledge, is not derived by the scientific method, and is not 'good science;' it is therefore inadmissible.").

[80] Nissen, ARCH INTERN MED, (June 2010) (published online) (Ex. 124).

[81] *Id.*

[82] Graham, et al, JAMA at E6 (Ex. 99).

study cannot address the question of causation, plaintiffs' experts misuse Dr. Graham's study to do precisely that.

G. Plaintiffs' Experts Rely On Findings That Are Not Statistically Significant

Courts applying *Daubert* have excluded as scientifically unreliable expert testimony based on findings that are not statistically significant.[83] Yet, plaintiffs' experts have relied on risk estimates in studies that are not statistically significant.[84] The reason for the exclusion of such testimony is that if there is an increase in the frequency of the disease but the increase is not statistically significant, then the possibility that the finding is the result of chance cannot be ruled out. For this reason, an association that is not statistically significant does not support the hypothesis that the exposure can cause the disease.[85]

H. Plaintiffs' Experts Applied A Clinical Standard, Not A Scientific Causation Standard, In Arriving At Their Opinions

Many of plaintiffs' experts merely applied a clinical standard in concluding that Avandia could cause heart attack. As plaintiffs' expert Dr. Septimus wrote in his report:

> Some might argue that randomized controlled trials have failed to show a statistically significant increase in CV events. *When acting as a pure scientist, one has the luxury and responsibility to look at results in a purely statistical fashion prior to drawing conclusions.* As a clinician,

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[83] *See Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 145-46, 118 S. Ct. 512 (1997) (evaluating reliability of epidemiological data based on statistical significance); *In re TMI Litig.*, 193 F.3d 613, 663 (3d Cir. 1999); *Pritchard v. Dow Agro Sciences*, 2010 U.S. Dist. LEXIS 23098, at *49-51 (W.D. Pa. Mar. 11, 2010) (excluding as unreliable expert's opinion based on studies that did not find statistically significant association); *Perry v. Novartis Pharm. Corp.*, 564 F. Supp. 2d 452, 465 (E.D. Pa. 2008) (same); *Soldo*, 244 F. Supp. 2d at 533 ("Courts have emphasized that epidemiologic proof must be statistically significant."); *Wade-Greaux*, 874 F. Supp. at 1451-1452 ("None of these studies shows a statistically significant increase in the risk of limb malformations associated with the use of any of the ingredients of Primatene® Tablets or Mist. As a result, none of these studies is the type of data upon which the scientific community would reasonably rely to draw [causal conclusions]").

[84] *See e.g.*, GSK's Motions to Exclude the General Causation Testimony of Drs. Lippman (Part A(3)); Swirsky (Part III); Brinton (Part V); Sniderman (Part A(1)).

[85] *Reference Manual* at 359-60 (Ex. 128).

> however, we must look at all the evidence before us and determine what is clinically significant. The trends towards increased CV events with Avandia, especially in patients taking insulin and nitrates and in those over age 65, are clinically significant regardless of the statistical p value.[86]

Similar statements appear in other experts' reports or deposition testimony.[87]

Plaintiffs' experts simply disregard the scientific methodology for establishing causation because they cannot establish causation under that standard. This is not what *Daubert* requires. When it comes to proving causation, the "clinical significance" standard does not satisfy the requirements of *Daubert* because it does not provide "sufficient, reliable scientific evidence to support a jury finding of legal causation."[88] As one district court explained:

> Basically, Plaintiffs seek to survive Defendant's Motions to Exclude and for Summary Judgment by emphasizing that they have employed the same methodology as is applied by doctors throughout the world in their clinical practices. Plaintiffs argue that they have used the best methodology available for this case. That may be so, but their methodology does not satisfy the requirements of Daubert. They have not provided sufficient, reliable scientific evidence to support a jury finding of legal causation.

Siharath v. Sandoz Pharms. Corp., 131 F. Supp. 2d 1347, 1372 (N.D. Ga. 2001).

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[86] Generic Expert Report of Joshua Septimus, M.D., Jan. 15, 2010 ("Septimus Report"), at 34 (attached as Exhibit 14) (emphasis added). The p value mentioned by Dr. Septimus is a measure of statistical significance.

[87] *See, e.g.*, Brinton Dep. Tr. at 37-40 (Ex. 37); Swirsky Dep. Tr. at 92 (Ex. 47); Lippman Dep. Tr. at 103-105 (Ex. 43); Deposition transcript of Allan Sniderman, M.D., Mar. 26, 2010. ("Sniderman Dep. Tr."), at 284 (Ex. 46); DePace Dep. Tr. at 140 (Ex. 39).

[88] *Siharath v. Sandoz Pharm. Corp.*, 131 F. Supp. 2d 1347, 1372 (N.D. Ga. 2001); *Norris v. Baxter Healthcare Corp*., 397 F.3d 878, 887 (10th Cir. 2005) ("We cannot allow the jury to speculate based on an expert's opinion which relies only on clinical experience in the absence of showing a consistent, statistically significant association between breast implants and systemic disease"); *Hollander v. Sandoz Pharms. Corp.*, 289 F.3d 1193, 1213 (10th Cir. 2002) (affirming exclusion of plaintiffs' experts whose causation opinions were based on "speculative leaps," notwithstanding the fact that "[t]he data on which they rely might well raise serious concerns in conscientious clinicians seeking to decide whether the benefits of the drug outweigh its risks").

I. Plaintiffs' Experts Lack A Reliable Theory For a Mechanism Of Action

Plaintiffs offer no coherent theory, let alone proof, of a mechanism by which Avandia causes the alleged increase in the risk of heart attack. The absence of a reliable explanation of the mechanism by which Avandia allegedly increases the risk of heart attack, coupled with the other flaws in their approach, renders plaintiffs' experts' conclusions scientifically unreliable and inadmissible.[89]

By way of example, Drs. Septimus and Sniderman claim that Avandia increases the level of Apo lipoprotein-B (apoB), a component of LDL cholesterol, which they say causes atherosclerosis.[90] Dr. Septimus claims that Avandia also increases the level of an inflammatory marker called lipoprotein-associated phospholipase A2 (LpPLA2), which he says causes increased instability of coronary plaque.[91] The problem with these claims is that they are simply theories without reliable proof. There are no outcome studies linking increases in apoB, LDL, or LpPLA2 in patients taking Avandia to an increased incidence of cardiovascular events. This point was driven home by the FDA's Dr. David Hoberman at the July 2010 Ad Com. He noted that there was no relationship between cardiovascular adverse events and LDL levels in the RECORD trial: "But the striking thing about this slide is that *those who did have events had*

[89] *See McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1253 (11th Cir. 2005) (experts failed to offer reliable explanation of the physiological process by which Metabolife causes heart attacks and ischemic strokes, i.e., establish general causation); *In re Accutane Prods. Liab.*, 511 F. Supp. 2d 1288, 1295 (M.D. Fla. 2007), ("a biological explanation without evidence of the mechanism by which it works is merely an unproven hypothesis, a theory", citing *Reference Manual*).

[90] Generic Expert Report of Allan Sniderman, M.D., Jan. 15, 2010 ("Sniderman Report"), at 3-9 (attached as Exhibit 16); Generic Expert Report of Joshua Septimus, M.D., Jan. 15, 2010 ("Septimus Report"), at 15-19 (attached as Exhibit 14).

[91] Septimus Report at 14 (Ex. 14).

virtually the same LDLs over time as those who did not have events, and in some cases, even lower."[92]

Plaintiffs' experts acknowledge that it is not scientifically reliable to infer from the way a drug affects a particular biomarker that the drug will have any specific effect on the cardiovascular outcomes of patients who take it; rather, outcome studies are needed to make a reliable determination of the drug's actual effect.[93] In fact, drugs that increase LDL may have decrease cardiovascular outcomes (fish oil), and drugs that decrease LDL may increase cardiovascular outcomes (torcetrapib). Not only have plaintiffs' experts not shown that patients who experience a heart attack while taking Avandia are the same patients who had increases in LDL or apo-B, they have not even attempted to show such a correlation. Plaintiffs' experts nevertheless assume their theories to be true,[94] while acknowledging the need for more data to test those theories.[95]

J. The Available Studies Show No Correlation between Avandia and Atherosclerosis

Because it is well-established that heart attack is caused by atherosclerosis, if Avandia did in fact increase the risk of heart attack, a progression in atherosclerosis in patients treated with Avandia would be expected. But five long-term RCTs evaluating atherosclerosis progression in patients treated with Avandia (VICTORY, STARR, APPROACH, PPAR, and

[92] July 14 Ad Com Tr., pp. 76-77 (Ex. 71).

[93] Deposition transcript of Joshua Septimus, M.D., Mar. 17, 2010, ("Septimus Dep. Tr.") at 370 (attached as Exhibit 45); Swirsky Dep. Tr. at 162:12-17 (Ex. 47).

[94] Septimus Report at 8 (Ex. 14); Sniderman Report at 4 (Ex. 16).

[95] Septimus Dep. Tr. at 375-76 (Ex. 45); Brinton Dep. Tr. at 181 (Ex. 37). Moreover, because plaintiffs' experts do not link the presumed effects of Avandia on cholesterol and other biomarkers to any particular plaintiff who had a heart attack, their theories also do not support an opinion as to specific causation.

Hedblad, et al.) found either no effects or beneficial effects on atherosclerosis progression and no increased risk of heart attack.[96] Plaintiffs' expert Dr. Brinton testified that there is no "randomized controlled trial, looking at atherosclerosis progression, in which there is a statistically significant increase in atherosclerosis progression with Avandia."[97]

[96] Bertrand et al. for the VICTORY Trial Investigators, *Cardiometabolic effects of rosiglitazone in patients with type 2 diabetes and coronary artery bypass grafts: A randomized placebo-controlled clinical trial*, ATHEROSCLEROSIS 2010 Aug;211(2):565-573. Epub 2010 Jun 11 (attached as Exhibit 56); Bhatt et al, *Peroxisome proliferator-activated receptor agonists for the prevention of adverse events following percutaneous coronary revascularization – results of the PPAR study*, 154 AM. HEART J. 137 (2007) (attached as Exhibit 58); Gerstein HC, Ratner RE, Cannon CP, Serruys PW, García-García HM, van Es GA, Kolatkar NS, Kravitz BG, Miller DM, Huang C, Fitzgerald PJ, Nesto RW; APPROACH Study Group, *Effect of rosiglitazone on progression of coronary atherosclerosis in patients with type 2 diabetes mellitus and coronary artery disease: the assessment on the prevention of progression by rosiglitazone on atherosclerosis in diabetes patients with cardiovascular history trial*, CIRCULATION 2010 Mar 16;121(10):1176-87. Epub 2010 Mar 1 (attached as Exhibit 97); B. Hedblad, et al., *Rosiglitazone and carotid IMT progression rate in a mixed cohort of patients with type 2 diabetes and the insulin resistance syndrome: main results from the Rosiglitazone Atherosclerosis Study*, JOURNAL OF INTERNAL MEDICINE 293 (2007) (attached as Exhibit 144); Eva M. Lonn *et al*., for the STARR Investigators, *Effect of ramipril and of rosiglitazone on carotid intima-media thickness in people with impaired glucose tolerance or impaired fasting glucose: STARR (Study of Atherosclerosis with Ramipril and Rosiglitazone),* 53 (22) J. AM. COLL. CARDIOL. 2028 (2009) (attached as Exhibit 114).

[97] Brinton Dep. Tr. at 284 (Ex. 37); Swirsky Dep. Tr. at 153-54 (Ex. 47) (acknowledging that he is not aware of any "data or trials or literature suggesting that Avandia contributed to the progression of atherosclerosis.").

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Respectfully submitted,

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APPENDIX I

I. THE ROLE OF EPIDEMIOLOGICAL STUDIES IN EVALUATING CAUSATION.

As described in the *Reference Manual on Scientific Evidence* (Fed. Jud. Ctr. 2d ed. 2000) (hereafter, "*Reference Manual*"), properly designed and executed epidemiological studies enable epidemiologists to assess the existence and strength of an association between an exposure and a disease.[1] "Epidemiology is the primary generally accepted methodology for demonstrating a causal relation between a chemical compound and a set of symptoms or a disease."[2] Epidemiological studies cannot directly assess cause; rather, they assess only whether a particular exposure is *associated* with a particular condition or disease. "It is axiomatic that "*an association is not equivalent to causation*."[3] "Evidence of an association may be sufficient for formulation of a hypothesis that can later be tested and confirmed, but it is not proof of causation in the courtroom or the scientific community."[4]

1. Types of epidemiological studies

Epidemiological studies are either experimental or observational. A randomized clinical trial or RCT is "an experimental study in which subjects are randomly assigned to one of two groups: one group exposed to the agent of interest and the other not exposed." Because randomization is "the best way to ensure that any observed difference between the two groups in

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[1] *Reference Manual* at 335-37 (Ex. 128).

[2] *Soldo v. Sandoz Pharm. Corp.*, 244 F. Supp. 2d 434, 532 (W.D. Pa. 2003) (citation omitted).

[3] *Reference Manual* at 335-36 (Ex. 128) (emphasis in original); *Norfolk & W. Railway Co. v. Ayers*, 538 U.S. 135, 173 (2003) ("Correlation is not causation"); *Norris v. Baxter Healthcare Corp.*, 397 F.3d 878, 885 (10th Cir. 2005) ("A correlation does not equal causation"); *Allison v. McGhan Med. Corp.*, 184 F.3d 1300, 1315 n.16 (11th Cir. 1999) ("showing *association* is far removed from proving causation"); *Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F. Supp. 2d 584, 591 (D.N.J. 2002) (same), *aff'd*, 68 F. App'x 356 (3d Cir. 2003).

[4] *Nelson v. American Home Products Corp.*, 92 F. Supp. 2d 954, 969 (W.D. Mo. 2000).

outcome is likely to be the result of exposure to the drug," RCTs are considered "the gold standard for determining the relationship of an agent to a disease or health outcome."[5]

Most epidemiological studies are observational: "that is, they 'observe' a group of individuals who have been exposed to an agent of interest . . . and compare them with another group of individuals who have not been so exposed."[6] Unlike RCTs and other experimental studies, observational studies cannot directly control for factors other than the exposure that may contribute to the relationship under study, and such confounding factors must therefore be considered in interpreting the results of observational studies.[7]

2. Identifying a statistically significant association

To determine the existence and strength of an association between an exposure and a disease, epidemiologists utilize a risk estimate (known as the "relative risk" in a cohort study, the "odds ratio" in a case-control study, and the "hazard ratio" in an RCT). If the relative risk equals 1.0, the risk in the exposed individuals is the same as the risk in the unexposed. If the relative risk is greater than 1.0, the risk in the exposed individuals is greater than the risk in the unexposed. Correspondingly, if the relative risk is less than 1.0, the risk in the exposed individuals is less than the risk in the unexposed.[8]

Epidemiologists express the degree of precision of a study's findings in terms of its "confidence interval." This is usually discussed in terms of whether the risk estimate is "statistically significant." The risk estimate is not statistically significant if the confidence

[5] *Reference Manual* at 338 (Ex. 128). *See also* Austin Dep. Tr. at 196 (Ex. 36); Brinton Dep. Tr. at 301 (Ex. 37).

[6] *Reference Manual* at 339 (Ex. 128).

[7] *Id.*

[8] *Id.* at 349.

interval includes the value 1.0, because the data then are consistent with no increased or decreased risk.[9] If the upper and lower bounds of the confidence interval are *both* greater than 1.0 (or both lower than 1.0), then the risk estimate is statistically significant.[10]

If there is an increase in the frequency of the disease but the increase is not statistically significant, then the possibility that the finding is the result of chance cannot be ruled out. For this reason, an association that is not statistically significant does not support the hypothesis that the exposure can cause the disease.[11]

3. Eliminating bias and confounding

Even if a statistically significant association is identified in a study, epidemiologists do not conclude that the association is real without examining the possibility that it is due to bias or confounding.[12] "If an association between the putative risk factor and the outcome is judged to exist, then the next step is to evaluate whether or not *alternative mechanisms* can explain it or not."[13] "This evaluation must be undertaken before a causal association can be inferred . . . ."[14]

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[9] *Id.* at 361.

[10] *Id.* Some courts have addressed statistical significance in terms of a different but related measure called the "probability" or "*p*" value. The conventional criterion for statistical significance is a p value <0.05, which means that the probability that the association observed is due to chance is less than 5 percent. *See DeLuca v. Merrell Dow Pharms., Inc*, 911 F.2d 941, 946-47 (3d Cir. 1990); *Wade-Greaux v. Whitehall Labs., Inc.*, 874 F. Supp. 1441, 1452 (D.V.I. 1994), *aff'd*, 46 F.3d 1120 (3d Cir. 1994).

[11] *Reference Manual* at 359-60 (Ex. 128).

[12] *Reference Manual* at 354 (Ex. 128); *Magistrini*, 180 F. Supp. 2d at 604 ("When evaluating the internal validity of a study, the researcher or scientist must account for the roles of bias, confounding factors, and the likelihood that the observed association is due to chance. This evaluation must be undertaken before a causal association can be inferred . . . .").

[13] Austin Report at 2 (Ex. 1) (emphasis in original).

[14] *Magistrini*, 180 F. Supp. 2d at 604.

4. From association to causation

If bias and confounding are eliminated as possible explanations for the statistically significant association, then it can be concluded that the exposure and the condition are actually associated – *i.e.*, that there is an association between the exposure and an increased risk of the condition. But additional steps are still required before it can be concluded that the association is *causal* — "it is not prudent to conclude that . . . a causal association, is the explanation without some positive evidence."[15]

Scientists use established criteria to determine whether such evidence exists.[16] "These criteria are sometimes referred to as the Bradford Hill criteria, after the author of a leading statement of the principles."[17] The Bradford Hill criteria include: (i) temporal relationship; (ii) strength of the association; (iii) dose-response relationship; (iv) replication of the findings; (v) biological plausibility; (vi) alternative explanations; (vii) cessation of exposure; (viii) specificity of the association; and (ix) consistency with other knowledge.[18] Courts applying *Daubert* routinely exclude expert testimony that proceeds from a finding of an association to a finding of causation without applying the Bradford Hill or similar criteria to determine whether the association is causal.[19]

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[15] Austin Report at 10 (Ex. 1).

[16] *Id.*

[17] *Amorgianos v. National R.R. Pass. Corp.*, 137 F. Supp. 2d 147, 168 (E.D.N.Y. 2001), *aff'd*, 303 F.3d 256 (2d Cir. 2002).

[18] *Reference Manual* at 374-79 (Ex. 128).

[19] *See Gannon v. United States*, 571 F. Supp. 2d 615, 640 (E.D. Pa. 2007) (rejecting general causation testimony by expert who admitted that Bradford Hill criteria were not met), *aff'd*, 292 F. App'x 170 (3d Cir. 2008); *Miller v. Pfizer Inc.*, 196 F. Supp. 2d 1062, 1078 (D. Kan. 2002) (excluding causation testimony of expert who misapplied Koch's postulates, criteria comparable to the Bradford Hill criteria), *aff'd*, 356 F.3d 1326 (10th Cir. 2004); *In re Breast Implant Litig.*, 11 F. Supp. 2d 1217, 1234 n.5 (D. Colo. 1998) ("Plaintiffs' causation experts

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must still satisfy the additional Bradford-Hill criteria to establish scientific cause and effect. Plaintiffs' experts have not addressed the Bradford-Hill criteria at all.").

APPENDIX II

I. EPIDEMIOLOGICAL STUDIES RELATING TO AVANDIA AND MI.

A. The Nissen meta-analysis

The Nissen 2007 meta-analysis[1] pooled data from 42 trials that compared patients treated with Avandia in various doses, sometimes as monotherapy and sometimes in combination with other drugs, to patients treated with an array of potential controls. The 42 trials consisted of 40 small, mostly short-term trials plus findings from the large, long-term DREAM and ADOPT trials described below. When the trials were analyzed separately, no statistically significant increase in the risk of MI was observed in patients treated with Avandia. However, when the data were combined, the Nissen authors reported that Avandia increased the risk of MI by a factor of 1.43 (95% CI 1.03-1.98). This meta-analysis excluded trials that reported zero adverse events, which had the effect of inflating the risk ratios.[2] The Nissen authors did not conclude that Avandia causes MI; they recommended, rather, that "patients and providers should carefully consider the *potential* risks of rosiglitazone in the treatment of type 2 diabetes."[3]

A meta-analysis is not a clinical study; it is, rather, a retrospective analysis that looks for statistical associations by pooling data from different studies that may differ in terms of design, purpose and endpoints.[4] The findings of a meta-analysis are therefore less reliable than

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[1] Steven E. Nissen & Kathy Wolski, *Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes*, 356 (24) *New Eng. J. Med.* 2457 (2007) (Ex. 123).

[2] The Singh meta-analysis, which pooled data from four long-term clinical trials, including data from the DREAM trial, unadjudicated data from the ADOPT trial and interim results from the RECORD trial (described below), found a statistically significant increased risk of MI in the same range as Nissen (RR 1.42 95% CI 1.06-1.91). *See* Singh S, Loke YK, Furberg CD, *Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis*, JAMA 2007;298(10):1189-95 (attached as Exhibit 131). This was not surprising given that, as plaintiffs' experts acknowledge, the data that were analyzed in the Singh meta-analysis largely overlapped the Nissen data.

[3] Nissen, 356 NEJM at 2470 (emphasis added) (Ex. 123).

[4] *Reference Manual* at 380 (Ex. 128).

those of a well-designed RCT. As stated in the *Reference Manual*, the problems of meta-analysis "have been so frequent and so deep, and overstatements of conclusions so extreme, that one might well conclude that there is something seriously and fundamentally wrong with the method."[5]

In addition to the general limitations of meta-analysis, the characteristics of the specific trials that were the source of the data considered in the Nissen meta-analysis further limited the conclusions that could be drawn. As the Nissen authors themselves pointed out, they

> pooled the results of a group of trials that were not originally intended to explore cardiovascular outcomes. Most trials did not centrally adjudicate cardiovascular outcomes, and the definitions of myocardial infarction were not available. Many of these trials were small and short-term, resulting in few adverse cardiovascular events or deaths. Accordingly, the confidence intervals for the odds ratios for myocardial infarction and death from cardiovascular causes are wide, resulting in considerable uncertainty about the magnitude of the observed hazard. Furthermore, we did not have access to original source data for any of these trials. . . . The lack of availability of source data did not allow the use of more statistically powerful time-to-event analysis.[6]

The increased risk of MI reported in the Nissen meta-analysis (43%) was, moreover, relatively low, and as the *Reference Manual* states, low relative risks must be scrutinized "more closely because there is a greater chance that they are the result of uncontrolled confounding or biases."[7]

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[5] *Reference Manual* at 381 n.127 (Ex. 128) (quoting John C. Bailar III, *Assessing Assessments*, 277 SCIENCE 528, 529 (1997)).

[6] Nissen, 356 NEJM at 2469 (emphasis added) (Ex. 123).

[7] *Reference Manual* at 376-377 (Ex. 128). As Dr. Austin's testimony (Austin Dep. Tr. at 50-52, Ex. 36) shows, this does not mean that patients who take Avandia have a 43% risk of having a heart attack. If a person's "background" risk of MI were 2% (*i.e.*, 2 chances in 100), the risk, if Nissen's 1.43 hazard ratio were correct, would be 1.43 times 2%, or 2.86% (*i.e.*, 2.86 chances in 100).

In 2010, Nissen and Wolski updated their 2007 meta-analysis with 14 additional trials ("Nissen 2010"). Compared to the 2007 meta-analysis, the updated Nissen meta-analysis reports a lower risk of MI (OR 1.28; 95% CI 1.02 – 1.63) and no increased risk of cardiovascular mortality (OR 1.03; 95% CI 0.78 – 1.36). Nowhere does the Nissen 2010 meta-analysis assert that Avandia causes myocardial infarction or cardiovascular death. Instead, the authors say the findings merely "suggest an unfavorable benefit to risk ratio for rosiglitazone use."[8]

The Nissen meta-analysis has been widely criticized as overstating the cardiovascular risks of Avandia.[9] In addition, the Nissen authors acknowledged that "a meta-analysis is always less convincing than a large, prospective trial designed to assess the outcome of interest" and that the RECORD trial (described below), "may provide useful insights."[10] As discussed below, the hypothesis of increased risk suggested by the Nissen meta-analysis is not substantiated by RECORD and other studies.

1. Large, long-term prospective RCTs

The best way to evaluate whether a drug is related to an outcome is to test that hypothesis through large, long-term prospective RCTs, the kind of study that, as noted

[8] Niseen, ARCH INTERN MED at E10 (Ex. 124).

[9] Editors of The Lancet, *Rosiglitazone: seeking a balanced prospective*, 369 THE LANCET 1834 (2007) (attached as Exhibit 49) ("it would be premature to overinterpret a meta-analysis that the authors and the NEJM all acknowledged contain important weaknesses"); R.W. Bilous, *Rosiglitazone and myocardial infarction: cause for concern or misleading meta-analysis?*, 24 DIAB. MED. 931, 932 (2007) (attached as Exhibit 60) (calling Nissen's meta-analysis "deeply flawed"); Valentin Fuster & Michael E. Farkouh, *Faster publication isn't always better*, 4 NATURE CLINICAL PRACTICE: CARDIOVASCULAR MED. 345, 345 (2007) (attached as Exhibit 95) (characterizing Nissen's analysis as "rushed and incomplete"); *see also* G. A. Diamond et al., *Uncertain effects of Rosiglitazone on the risk of myocardial infarction and cardiovascular death*, 147 ANN. INTERN. MED. 578 (2007) (attached as Exhibit 66) (conducting several meta-analyses on the same data used in the Nissen meta-analysis, and concluding that Nissen's meta-analysis "probably exaggerated risk estimates," and led to "confusing and conflicting results about cardiovascular risk associated with rosiglitazone therapy"); Z.T. Bloomgarden, *The Avandia Debate*, 30 DIABETES CARE 2401, 2405-06 (2007) (attached as Exhibit 61) (commenting that Dr. Nissen's paper violated standard meta-analysis methodology by failing to start with a pre-specified study hypothesis, leading to "data snooping on quite a large scale," and concluding that it is a "poor basis for making decisions.").

[10] Nissen, 356 NEJM at 2469 (Ex. 123).

previously, scientists consider the "gold standard." Three such trials of Avandia have been conducted; *none showed a statistically significant increased risk of MI.*

a. The RECORD trial[11]

The RECORD trial tracked cardiovascular outcomes over 5-7 years of follow-up by comparing patients taking Avandia plus one of two other anti-diabetic drugs to patients taking the two other drugs in combination. The primary endpoint (the outcome the trial was powered to measure) in RECORD was hospitalization or death from cardiovascular causes; secondary endpoints were specified cardiovascular events, including MI. Unlike the underlying trials in the Nissen and Singh meta-analyses**,** all endpoint data were adjudicated by independent evaluators blinded to the treatment received.[12]

The RECORD trial showed no increased risk of cardiovascular death or hospitalization, and no statistically significant increase in the risk of MI, in the patients treated with Avandia as compared to the controls (HR 1.14; 95% CI 0.80 – 1.63).[13]

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[11] Philip D. Home *et al*., for the RECORD Study Team, *Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomized, open-label trial*, 373 (9681) LANCET 2125 (2009) (attached as Exhibit 105).

[12] Although one FDA reviewer of RECORD at the 2010 AdCom meeting (Dr. Marciniak) criticized the adjudication process in RECORD and re-adjudicted the findings, his criticisms and re-adjudciation were not validated by other FDA reviewers. In fact, the FDA's Division of Scientific Investigations examined Dr. Marciniak's concerns and found no systemic or pervasive findings that would undermine the reliability of the RECORD data. Moreover, Dr. Unger (Deputy Director of FDA's Office of Drug Evaluation) noted that Dr. Marciniak's unblinded re-adjudication of a subset of RECORD data was not performed according to FDA standard operating procedures and can only be considered "exploratory." Even after reviewing Dr. Marciniak's conerns and unblinded re-adjudication, Dr. Unger concluded that the RECORD results "do not substantiate the findings from the Nissen/Wolski meta-analysis on myocardial infarction and cardiovascular death." FDA Briefing Document for 7.13.10 & 7.14.10 Ad Com. Leibenhaut S to Mahoney KM, Parks MH - June 18, 2010, Summary of Inspections for NDA 21-071 Div. of Scientific Investigations (attached as Exhibit 84); FDA Briefing Document for 7.13.10 & 7.14.10 Ad Com. Unger EF to File - June 15, 2010, DMEP consulted DCaRP on the RECORD trial, Submitted as a Supplement to NDA 21-071 (attached as Exhibit 92).

[13] Notably, RECORD satisfies the current FDA guidelines for establishing the cardiovascular safety of new anti-diabetic therapies. *See* FDA Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. December 2008 (attached as Exhibit 94). This Guidance states that "to establish the safety" of a new antidiabetic therapy, sponsors should demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk. One way to demonstrate such safety is by conducting a (continued...)

b. The DREAM trial[14]

The Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial was a double-blind placebo-controlled trial in pre-diabetic patients designed to evaluate whether Avandia and/or ramipril (an ACE inhibitor indicated for prevention of cardiovascular disease) reduced the development of type 2 diabetes. The primary endpoint was a composite outcome consisting of the development of diabetes or death; secondary endpoints were a composite outcome of cardiovascular events including MI, and individual components of the composite outcome. After a three-year follow-up, patients treated with Avandia had a statistically significant reduction in progression to diabetes and/or death, and "both treatment groups had much the same frequency of the composite cardiovascular outcomes and of every component of the composite except of heart failure." There was no statistically significant increase in heart attack in patients taking Avandia.[15]

c. The ADOPT trial[16]

A Diabetes Outcome Progression Trial (ADOPT) was a double-blind trial in patients with newly-diagnosed diabetes to assess the effect of Avandia, as compared to other

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(continued...)

"single, large safety trial" showing that the upper bound of the 95% confidence interval for cardiovascular events is less than 1.3 (as noted above, the upper bound for the primary endpoint in the RECORD trial was 1.16).

[14] *See* Gerstein HC, Yusuf S, et al.; part of DREAM Trial Investigators, *Effect of Rosiglitazone on the Frequency of Diabetes in Patients with Impaired Glucose Tolerance or Impaired Fasting Glucose: A Randomized Controlled Trial*, 368 LANCET 1096 (2006) (attached as Exhibit 98).

[15] In DREAM, there was a non-significant decrease in the risk of heart attack in patients taking Avandia alone compared to patients taking placebo alone (OR 0.83; 95% CI 0.20 - 3.27). Food & Drug Administration, Dep't Health and Human Services, FDA Briefing Document: Advisory Committee Meeting for NDA 21-071 Avandia (July 13-14, 2010), Karen Mahoney, Preliminary Endocrine Medical Officer Review of the RECORD, and Update on Cardiovascular Safety Information from Large Clinical Trials of Rosiglitazone (June 9, 2010) (attached as Exhibit 85).

[16] *See* Steven E. Kahn et al., for the ADOPT Study Group, *Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy*, 355 NEW ENGL. J. MED. 2427 (2006) (attached as Exhibit 109).

standard glucose-lowering therapies**,** in maintaining long-term glycemic control. Adverse events, including MI, were identified from investigator reports, and GSK and FDA each computed hazard ratios based on these data. There was no statistically significant increase in heart attack in patients taking Avandia.

d. Other large, long-term, prospective RCTs

The BARI-2D[17], VADT[18] and ACCORD[19] trials evaluated the effect of glucose-lowering strategies on cardiovascular outcomes. Each of these trials used Avandia and conducted post-hoc analyses to assess the effect of Avandia on cardiovascular outcomes and mortality. Because these trials did not randomize patients to receive Avandia, the post-hoc analyses are observational. However, these trials were specifically designed to ascertain and adjudicate cardiovascular outcomes, and specifically captured information from participants relevant to cardiovascular outcomes, which shields the observational analyses from potential biases and confounding inherent in other observational studies.

No increased risk of MI or cardiovascular death was observed in patients taking Avandia in the BARI-2D[20] and VADT[21] trials. In fact, treatment with Avandia was associated

[17] The BARI-2D Study Group, *A Randomized Trial of Therapies for Type 2 Diabetes and Coronary Artery Disease*, 360 NEW ENGL. J. MED. 2503 (2009) (attached as Exhibit 55).

[18] Duckworth et al., Glucose *Control and Vascular Complications in Veterans with Type 2 Diabetes*, 360 NEW. ENGL. J. MED. 129 (2009) (attached as Exhibit 69).

[19] The Action to Control Cardiovascular Risk in Diabetes Study Group, *Effects of Intensive Glucose Lowering in Type 2 Diabetes*, 358 NEW ENGL. J. MED. 2545 (2008) (attached as Exhibit 50).

[20] Maria M. Brooks, Rosiglitazone Use and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Coronary Artery Disease in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Trial, *presented at* FDA Advisory Committee Meeting for NDA 21-071 Avandia (July 13-14, 2010) (attached as Exhibit 74).

[21] Thomas Moritz, Presentation at Food & Drug Administration Advisory Committee Meeting for NDA 21-071 Avandia, Impact of the use of Rosiglitazone in VADT (July 13-14, 2010) (attached as Exhibit 90).

with a lower risk of ischemic cardiovascular outcomes in these studies. ACCORD only assessed the effect of Avandia on mortality, but similarly found no increased risk.[22]

2. Other meta-analyses

In contrast to the Nissen meta-analysis, other meta-analyses have not shown a statistically significant association between Avandia and MI.

a. GSK and FDA meta-analyses

GSK conducted a meta-analysis of studies from the Avandia trial registry that was published in 2008 (this is referred to as the "ICT-42" meta-analysis). The ICT-42 meta-analysis synthesized 42 short-term trials that substantially overlapped the trials in the Nissen meta-analysis.[23] Like the Nissen meta-analysis, these trials were not designed prospectively to ascertain or adjudicate cardiovascular events. Unlike the Nissen meta-analysis, however, the ICT-42 meta-analysis included trials with zero events. Odds ratios for MI in comparisons of Avandia to various controls were not statistically significant (HR 1.59, 95% CI 0.93-2.71). The FDA analyzed the same data from ICT-42 and generated essentially the same non-statistically significant results for MI (HR 1.5, 95% CI 0.9-2.7).

In 2009, GSK updated the ICT-42 meta-analysis by adding data from ten additional studies that were not available at the time of the earlier analysis. This updated meta-analysis (known as ICT-52) also did not find an increased risk of MI associated with Avandia (HR 1.23, 95% CI 0.5-3.1). FDA also evaluated the ICT-52 using a different methodology than

[22] Michael E. Miller for Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study Group, Presentation at the 68th Annual Scientific Sessions of the American Diabetes Association: Relationship between glycemia medications and mortality in ACCORD (June 6-10, 2008) (attached as Exhibit 51).

[23] Cobitz A, Zambanini A, Sowell M, Heise M, Louridas B, McMorn S, Semigran M, Koch G, *A retrospective evaluation of congestive heart failure and myocardial ischemia events in 14,237 patients with type 2 diabetes mellitus enrolled in 42 short-term, double-blind, randomized clinical studies with rosiglitazone*, 17(8) PHARMACOEPIDEMIOL DRUG SAF 769 (2008) (attached as Exhibit 65).

GSK and reported a different result. FDA reported a statistically significant increased risk of MI (OR 1.80; CI 1.03 – 3.25).[24] Like GSK, FDA found no statistically significant increased risk of MACE events (defined as cardiovascular death, stroke, or myocardial infarction), stroke events, or cardiovascular death.

Two other FDA and GSK meta-analyses are also of significance. The first was the result of a post-study adjudication by GSK of the MI events in ADOPT. FDA evaluated the adjudicated data from the DREAM, ADOPT and interim RECORD trials and found *no statistically significant increase in MI.*[25] The results of this meta-analysis appear in the FDA-approved labeling for Avandia and also in the clinical trial registry on GSK's website.

The second meta-analysis was a further meta-analysis by GSK using the adjudicated data from the DREAM and ADOPT trials and the final RECORD data. This meta-analysis, known as AVD 113985, likewise found *no statistically significant increase in MI* (HR 1.14, 95% CI 0.87-1.49).[26]

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[24] Brad McEvoy et al., FDA Rosiglitazone and Pioglitazone Meta-Analyses (June 15, 2010) *in* Food & Drug Administration, Dep't Health and Human Services, FDA Briefing Document: Advisory Committee Meeting for NDA 21-071 Avandia (July 13-14, 2010) (attached as Exhibit 87).

[25] AVD:28PI (current Avandia label) (attached as Exhibit 54).

[26] GlaxoSmithKline, 2009 Update to Integrated Cardiovascular (CV) Endpoint data from the Final Analyses for Studies BRL-049653/048 (ADOPT), AVD107642 (DREAM), and BRL-049653/231 (RECORD) (Study No.: AVD113985) (attached as Exhibit 135).

b. Diamond,[27] Monami[28] and Mannucci[29] meta-analyses

Several other meta-analyses likewise have not found a statistically significant increased risk of MI in patients treated with Avandia.

The Diamond meta-analysis published in 2007, analyzed the same data as Nissen, but using different statistical methods. The results were different: the Diamond authors found no statistically significant increased risk of MI using six different statistical models.

The Monami meta-analysis, published in 2008, synthesized data from 86 clinical trials. Although the Monami authors excluded trials with zero events just as the Nissen authors did, they nevertheless did not find a statistically significant association between Avandia and MI.

The authors of the Mannucci meta-analysis, published in 2009, noted that the Nissen authors had not included data from all of the clinical trials of Avandia that were available at the time that meta-analysis was conducted. The authors accordingly collected "all available evidence from published or unpublished randomized clinical trials," and their meta-analysis included 164 clinical trials, nearly four times more than the 42 trials included in the Nissen meta-analysis. The Mannucci authors found no statistically significant association between Avandia and MI, and they concluded, contrary to Nissen, that "there is no evidence of increased risk of myocardial infarction or cardiovascular mortality in patients treated with rosiglitazone."

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[27] Diamond GA, Bax L, Kaul S, *Uncertain effects of rosiglitazone on the risk for myocardial infarction and cardiovascular death*, 147 ANN INTERN MED 578 (2007) (attached as Exhibit 66).

[28] Monami M, Marchionni N, Mannucci E., *Winners and losers at the rosiglitazone gamble A meta-analytical approach at the definition of the cardiovascular risk profile of rosiglitazone*, 82 DIABETES RES CLIN PRACT 48 (2008) (attached as Exhibit 118).

[29] Edoardo Mannucci et al., *Cardiac safety profile of rosiglitazone: A comprehensive meta-analysis of randomized clinical trials*, INT. J. CARDIOL., e-publication (2009) (attached as Exhibit 115).

3. RCTs have shown that Avandia does not advance the progression of atherosclerosis

Five RCTs evaluating atherosclerosis progression in patients treated with Avandia found either no effects or beneficial effects on atherosclerosis progression and no increased risk of MI.[30]

The VICTORY trial[31] is a double-blind, placebo-controlled RCT evaluating whether Avandia prevents atherosclerosis progression 1-10 years after coronary bypass surgery. The primary endpoint was a change in plaque volume in the sapphenous vein graft (used to bypass the coronary blockage), and MI was one of the secondary endpoints. After 12 months of follow-up, treatment with Avandia did not result in a statistically significant change in sapphenous vein plaque volume compared to placebo. Treatment with Avandia was associated with statistically significant benefits in specific lipid parameters, including an increase in HDL cholesterol and a decrease in the percentage of small, dense, atherogenic LDL cholesterol.

The APPROACH trial[32] is a double-blind RCT comparing the effects of rosiglitazone to those of glipizide (a sulfonylurea) on progression of atherosclerosis in coronary arteries in patients with diabetes and cardiovascular disease. After 18 months of follow-up, the

[30] Because it is well-established that MI is caused by atherosclerosis, if Avandia did in fact increase the risk of MI, one would expect to see a progression in atherosclerosis in patients treated with Avandia.

[31] Bertrand et al. for the VICTORY Trial Investigators, *Cardiometabolic effects of rosiglitazone in patients with type 2 diabetes and coronary artery bypass grafts: A randomized placebo-controlled clinical trial*, ATHEROSCLEROSIS 2010 Aug;211(2):565-573. Epub 2010 Jun 11 (attached as Exhibit 56).

[32] Gerstein HC, Ratner RE, Cannon CP, Serruys PW, García-García HM, van Es GA, Kolatkar NS, Kravitz BG, Miller DM, Huang C, Fitzgerald PJ, Nesto RW; APPROACH Study Group, *Effect of rosiglitazone on progression of coronary atherosclerosis in patients with type 2 diabetes mellitus and coronary artery disease: the assessment on the prevention of progression by rosiglitazone on atherosclerosis in diabetes patients with cardiovascular history trial*, CIRCULATION 2010 Mar 16;121(10):1176-87. Epub 2010 Mar 1 (attached as Exhibit 97).

results showed a non-statistically significant reduction in atherosclerosis progression in the patients treated with Avandia and no statistically significant difference in the incidence of MI.

The STARR trial[33] was a sub-study within the DREAM trial. The primary endpoint was progression of aggregate carotid intima thickness, an indication of atherosclerosis in the carotid arteries. The authors concluded that

> the results for rosiglitazone are not conclusive but suggest a modest beneficial effect on vascular disease progression. This could result in more robust long-term effects on vascular disease progression and possibly on clinical ischemic events, although this hypothesis requires further evaluation.

The PPAR trial[34] is a double-blind, placebo controlled trial evaluating progression of carotid intima medial thickness in patients with metabolic syndrome and coronary artery disease. After 12 months of follow-up, there was no statistically significant difference between Avandia and placebo on progression of carotid intima medial thickness.

The Rosiglitazone Atherosclerosis Study[35] is a double-blind, placebo controlled study evaluating progression of carotid intima medial thickness in patients with insulin resistance or type 2 diabetes. After 52 weeks of follow-up, there was no statistically significant difference between Avandia and placebo on the primary measure of atherosclerosis progression. Secondary measures of atherosclerosis suggested a benefit of Avandia on atherosclerosis progression.

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[33] Eva M. Lonn *et al.*, for the STARR Investigators, *Effect of ramipril and of rosiglitazone on carotid intima-media thickness in people with impaired glucose tolerance or impaired fasting glucose: STARR (Study of Atherosclerosis with Ramipril and Rosiglitazone)*, 53 (22) J. AM. COLL. CARDIOL. 2028 (2009) (attached as Exhibit 114).

[34] Bhatt et al, *Peroxisome proliferator-activated receptor agonists for the prevention of adverse events following percutaneous coronary revascularization – results of the PPAR study*, 154 AM. HEART J. 137 (2007) (attached as Exhibit 58).

[35] B. Hedblad, et al., *Rosiglitazone and carotid IMT progression rate in a mixed cohort of patients with type 2 diabetes and the insulin resistance syndrome: main results from the Rosiglitazone Atherosclerosis Study*, JOURNAL OF INTERNAL MEDICINE 293 (2007) (attached as Exhibit 144).

In short, none of these five RCTs showed an association between Avandia and progression of atherosclerosis.

4. Observational studies

There are twenty-three observational studies that have assessed the possible relationship between Avandia and heart attack. The reported findings are inconsistent and inconclusive: nine showed a statistically significant increased risk of heart attack compared to other oral anti-diabetic drugs or compared specifically to pioglitazone;[36] thirteen found no statistically significant association;[37] and one found a statistically significant *protective* association.[38]

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[36] Brownstein JS, et al, *Rapid identification of myocardial infarction risk associated with diabetes medications using electronic medical records*, 33 DIABETES CARE 526 (2010) (attached as Exhibit 62); Gerrits et al., *A Comparison of Pioglitazone and Rosiglitazone for Hospitalization for Acute Myocardial Infarction in Type 2 Diabetes*, 16 PHARMACOEPIDEMIOLOGY DRUG SAF. 1065 (2007) (attached as Exhibit 96); Hsiao, F. et al., *Thiazolidinediones and Cardiovascular Events in Patients with Type 2 Diabetes Mellitus: A Retrospective Cohort Study of Over 473,000 Patients Using the National Health Insurance Database in Taiwan*, 32 DRUG SAFETY 675 (2009) (attached as Exhibit 106); Koro CE, Fu Q, Stendar M. *An assessment of the effect of thiazolidinedione exposure on the risk of myocardial infarction in type 2 diabetic patients*, 17 PHARMACOEPIDEMIOL DRUG SAF 989 (2008) (attached as Exhibit 111); Lipscombe et al., *Thiazolidinediones and cardiovascular outcomes in older patients with diabetes*, 298 JAMA 2634 (2007) (attached as Exhibit 113); Ramirez Sp, et al., *Rosiglitazone is associated with mortality in chronic hemodialysis patients*, 20 J AM SOC NEPHROL 1094 (2009) (attached as Exhibit 127); Shaya, F. et al., *Thiazolidinediones and Cardiovascular Events in High-Risk Patients with Type-2 Diabetes Mellitus*, 34 P&T 490 (2009) (attached as Exhibit 130); Vanasse, A., et al., *Stroke and Cardiovascular Morbidity and Mortality Associated with Rosiglitazone Use in Elderly Diabetic Patients*, 6 DIAB VASC DIS RES 87 (2009) (attached as Exhibit 138); Ziyadeh N, et al., *The thiazolidinediones rosiglitazone and pioglitazone and the risk of coronary heart disease: a retrospective cohort study using a US health insurance database*, 31 CLIN THER 2665 (2009) (attached as Exhibit 141).

[37] Bilik, D. et al., *Thiazolidinediones and Fractures: Evidence from Translating Research into Action for Diabetes*, 95 J CLIN ENDOCRINOL METAB 0000-0000 (2010) (attached as Exhibit 59); Casscells SW, et al., *A comparison of select cardiovascular outcomes by antidiabetic prescription drug classes used to treat type 2 diabetes among Military Health System beneficiaries, fiscal year 2003-2006*, 15 AM J THER 198 (2008) (attached as Exhibit 64); Dore DD, et al. *Association between extent of thiazolidinedione exposure and risk of acute myocardial infarction*, 29 PHARMACOTHERAPY 775 (2009) (attached as Exhibit 67); Dormuth CR, et al., *Rosiglitazone and myocardial infarction in patients previously prescribed metformin*, PLOS ONE (2009) (attached as Exhibit 68); Graham, DJ, et al., *Risk of Acute Myocardial Infarction, Stroke, Heart Failure, and Death in Elderly Medicare Patients Treated With Rosiglitazone or Pioglitazone*, 304(4) JAMA. 411 (2010) (attached as Exhibit 99); Habib ZA, et al., *Relationship between thiazolidinedione use and cardiovascular outcomes and all-cause mortality among patients with diabetes: a time-updated propensity analysis*, 18 PHARMACOEPIDEMIOL DRUG SAF 437 (2009) (attached as Exhibit 102); Juurlink DN, et al., *Adverse cardiovascular events during treatment with pioglitazone and rosiglitazone: population based cohort study*, 339 BMJ b2942 (2009) (attached as Exhibit 108); McAfee AT, et al., *Coronary heart disease outcomes in patients receiving antidiabetic agents*, 16 PHARMACOEPIDEMIOL DRUG SAF

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711 (2007) (attached as Exhibit 117); Pantalone KM, et al., *The risk of developing coronary artery disease or congestive heart failure, and overall mortality, in type 2 diabetic patients receiving rosiglitazone, pioglitazone, metformin, or sulfonylureas: a retrospective analysis*, 46 ACTA DIABETOL 145 (2009) (attached as Exhibit 125); Stockl KM, et al., *Risk of acute myocardial infarction in patients treated with thiazolidinediones or other antidiabetic medications*, 18 PHARMACOEPIDEMIOL DRUG SAF 166 (2009) (attached as Exhibit 134); Tzoulaki I, et al., *Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database*, 339 BMJ b4731 (2009) (attached as Exhibit 137); Walker AM, Koro CE, Landon J, *Coronary heart disease outcomes in patients receiving antidiabetic agents in the PharMetrics database 2000-2007*, 17 PHARMACOEPIDEMIOL DRUG SAF 760 (2008) (attached as Exhibit 139); Winkelmayer WC, et al., *Comparison of cardiovascular outcomes in elderly patients with diabetes who initiated rosiglitazone vs pioglitazone therapy*, 168 ARCH INTERN MED 2368 (2008) (attached as Exhibit 140).

[38] Margolis DJ, Hoffstad O, Strom BL, *Association between serious cardiac outcomes and medications used to treat diabetes*, 17 PHARMACOEPIDEMIOL DRUG SAF 753 (2008) (attached as Exhibit 116).

APPENDIX III

I. THE VIEWS OF PROFESSIONAL ORGANIZATIONS.

No professional organization has concluded that Avandia causes myocardial infarction. For example, in October 2008, the American Diabetes Association ("ADA") and the European Association for the Study of Diabetes ("EASD") published a treatment algorithm for the management of hyperglycemia in type 2 diabetes.[1] This algorithm was published after the Nissen meta-analysis but without the benefit of the completed RECORD trial. Although the authors recommended against using Avandia, they noted that meta-analyses had only "suggested" an increased risk of myocardial infarction and were "not conclusive regarding the potential cardiovascular risk associated with rosiglitazone."[2]

Similarly, in October 2009, with the benefit of the completed RECORD trial, the American Association of Clinical Endocrinologists ("AACE") and the American College of Endocrinology ("ACE") published a treatment algorithm for glycemic control in type 2 diabetes.[3] The authors of the AACE/ACE treatment algorithm recommend Avandia as an appropriate therapy in type 2 diabetes and drew no distinction between Avandia and pioglitazone with regard to cardiovascular risk.

Thereafter, in the January 2010 Standards of Medical Care in Diabetes issued by the American Diabetes Association, the only cautionary statement pertaining to Avandia related

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[1] D.M. Nathan *et al*., *Medical management of hyperglycemia in type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy*. 52 DIABETOLOGIA 17 (2009) (attached as Exhibit 120). The same report was published in Diabetes Care. 31(12) DIABETES CARE (2008).

[2] *Id*. at 22.

[3] Helena W. Rodbard *et al*., *Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: an algorithm for glycemic control*. 15 (6) ENDOCRINE PRACTICE 540 (2009) (attached as Exhibit 126).

to TZDs as a drug class and the risk of fluid retention and heart failure.[4] This evidence-based position statement was reviewed and approved by the Executive Committee of ADA's Board of Directors and is, therefore, the official position of the ADA.

Even more recently, in their Science Advisory on Thiazolidinedione Drugs and Cardiovascular Risks,[5] the American Heart Association and the American College of Cardiology Foundation referred to the "clinical equipoise" in the data on Avandia and myocardial ischemia and called on "academic researchers, industry and government agencies to collaborate on definitive randomized trials to answer [the] important clinical questions" raised by previous studies.

[4] American Diabetes Association. *Standards of medical care in diabetes -- 2010.* DIABETES CARE 2010;33 (Suppl 1):S11-61 (attached as Exhibit 53).

[5] Kaul S, Bolger AF, Herrington DM, Guigliano RP, Eckel RH. *Thiazolidinedione drugs and cardiovascular risks: a science advisory from the American Heart Association and the American College of Cardiology Foundation.* J AM COLL CARDIOL 2010;55 (attached as Exhibit 110).

CERTIFICATE OF SERVICE

I hereby certify that on August 9, 2010, I caused a true and correct copy of the foregoing Overview Memorandum on *Daubert* Issues Relating to General Causation to be served by electronic mail and Federal Express upon plaintiff's counsel as follows:

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